UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DATE: October 8, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **CADUSOFOS - *FQPA REQUIREMENT*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 10/8/97
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel 10/8/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Mike Metzger
Reregistration Branch 2
Health Effects Division (7509C)

PC Code: 128864

BACKGROUND: On September 23, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Cadusofos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Cadusofos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
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A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Cadusofos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Cadusofos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS

1. Neurotoxicity

- In an acute delayed neurotoxicity study, hens received an oral administration of a single dose of Cadusofos at 8 mg/kg/day. Cadusofos did not cause delayed neurotoxicity. However, the Committee noted neither histopathology nor neurotoxic esterase (NTE) activity was assessed in this study (MRID No. 00255691).

- No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, FOB, and histopathology on the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to Cadusofos.

2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity of young rats or rabbits following pre- or postnatal exposure to Cadusofos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Sprague-Dawley rats received oral doses of Cadusofos at 0, 2, 6 or 18 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 6 mg/kg/day and the LOEL was 18 mg/kg/day based on cholinergic signs including diarrhea, decreased locomotion, tremors, lacrimation, exothalmus and fasciculation. For developmental toxicity, the NOEL was 6 mg/kg/day and the LOEL was 18 mg/kg/day based on decreased fetal body weight. There was no evidence of teratogenicity (MRID No. 00159057).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of Cadusofos 0, 0.1, 0.3, or 0.9 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 0.3 mg/kg/day and the LOEL was 0.9 mg/kg/day based on mortality and clinical signs of toxicity including ataxia, dyspnea and prostration. For developmental toxicity, the NOEL was 0.3 mg/kg/day and the LOEL 0.9 mg/kg/day based on an increase in the total number of resorptions, a decrease in the total number of fetuses compared to controls and fetal death. There was no evidence of teratogenicity (MRID No. 00159058).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Cadusofos at 0, 0.1, 0.5 or 5 ppm (0, 0.005, 0.025, or 0.25 mg/kg/day) for two successive generations. There was no increased sensitivity to pups over the adults. The parental/ systemic NOEL was 0.5 ppm (0.025 mg/kg/day) and the LOEL was 5 ppm (0.25 mg/kg/ day) based on significant inhibition of plasma and red blood cell cholinesterase activity. For reproductive toxicity, the NOEL was 0.1 ppm (0.005 mg/kg/day) and the LOEL was 0.5 ppm (0.025 mg/kg/day) based on significant decrease in live birth index (MRID No. 41441803).

4. Cholinesterase Inhibition

- No data are available to compare the effects of Cadusofos on cholinesterase activity in the adults and/or pups since this endpoint was not evaluated in the developmental toxicity studies in rats and rabbits and was measured only in the parental animals in the 2-generation reproduction study. In addition, data gaps exists for acute and subchronic neurotoxicity studies.

5. Developmental Neurotoxicity

- Data available to assess the potential developmental neurotoxicity of Cadusofos are limited due to the lack of neurotoxicity (acute and subchronic) studies in rats as well as a hen study with neuropathology and NTE data. Therefore, the Committee decided to place the Guideline requirement for a developmental neurotoxicity study in *reserve status* until submission and review of the acute study in hen as well as the acute and subchronic neurotoxicity studies in rats.

6. Reference Dose (RfD)

- An RfD of 0.0005 mg/kg/day was derived from the NOEL of 0.05 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on tremors and inhibition of red blood cell and brain cholinesterase activity observed at 0.25 mg/kg/day in dogs in a chronic toxicity study. The UF of 100 included a 10 for intra-species and 10 for inter-species variation.

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7. Data Gaps

- Acute delayed neurotoxicity study in hen with neuropathology and NTE assessments.

- Acute and subchronic neurotoxicity studies in rats

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

An appropriate toxicological end point for acute dietary risk assessment can not be identified from the existing data base. The Committee noted the data gap for an acute neurotoxicity study.

For acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be retained**. Therefore, **a Margin of Exposure of 1000 is required** to ensure protection of this population from acute exposure to Cadusofos for reasons stated below:

(i) Lack of neuropathology and NTE data in the acute delayed neurotoxicity study in hen

(ii) Due to the lack of an acute neurotoxicity study data on cholinesterase inhibition and FOB as well as histopathology on the central and peripheral nervous system are not available for evaluation after a single exposure to Cadusofos.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on plasma cholinesterase inhibition observed at 0.005 mg/kg/day (LOEL) in dogs. The NOEL was 0.001 mg/kg/day. An UF of 100 (10 x each for inter and intra species variability) was applied to the NOEL to derive the RfD of 0.00001 mg/kg/day.

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For chronic dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** Therefore, **a total UF of 1000** (i.e., 10 for inter-species variation x 10 for intra-species variation x 10 for FQPA) **is required**. **Based on this the RfD is revised to 0.000001 mg/kg/day** and this is supported by the following factors:

(i) Lack of neuropathology and NTE data in the acute delayed neurotoxicity study in hen

(ii) Lack of acute and subchronic neurotoxicity studies in rats.

(iii) Lack of cholinesterase inhibition and FOB data as well as histopathology on the central and peripheral nervous system.

(iv) Lack of and evaluation of a critical endpoint (i.e., measurement of cholinesterase activity) in the developmental toxicity studies or in the pups in the reproduction study which would have yielded a comparison of this endpoint in adults and offspring.

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